SCIENTIFIC LETTER

Beneficial effect of short term intake of red wine polyphenols on coronary microcirculation in patients with coronary artery disease

T Hozumi, K Sugioka, K Shimada, S H Kim, M Y Kuo, Y Miyake, K Fujimoto, R Otsuka, H Watanabe, K Hosoda, J Yoshikawa, S Homma

Heart 2006;**92**:681–682. doi: 10.1136/hrt.2004.059204

Previous studies have shown the antioxidant effects of polyphenols in red wine.[1–4] An acute effect of red wine on the coronary microcirculation has been shown in healthy volunteers, although neither white wine nor vodka had an acute effect on coronary microcirculation in that study.[5] Thus, we hypothesised that the coronary microcirculation can be improved by a daily intake of red wine polyphenols without alcohol. In addition, this effect may be seen not only in the healthy person but also in the patient with coronary artery disease (CAD).

Recent advances in transthoracic Doppler echocardiography (TTDE) have enabled non-invasive assessment of coronary flow velocity reserve (CFVR) in the clinical setting.[6 7] This non-invasive technique has made serial assessment of CFVR after daily intake of red wine polyphenols possible even in patients with CAD. The purpose of this study was to evaluate the short term effect of taking red wine polyphenols on the coronary microcirculation by using TTDE to assess patients with CAD.

METHODS

Ten male patients with angiographically documented CAD were recruited for this study (mean (SD) age 61 (7) years, body mass index 28.5 (5.2) kg/cm^2) in New York, USA and Osaka, Japan from October 2000 to March 2002. Exclusion criteria were as follows: (1) anterior myocardial infarction (MI); (2) significant stenosis (> 50%) in the left anterior descending coronary artery; (3) recent MI (< 6 months); (4) severely disturbed cardiac function (ejection fraction < 40%); (5) uncontrolled hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 100 mm Hg); (6) uncontrolled diabetes (fasting blood glucose > 5.55 mmol/l) and uncontrolled hypercholesterolaemia (total cholesterol > 6.22 mmol/l); (7) daily intake of red wine (> 1 glass/day); (8) tobacco smoking; (9) consumption of vitamin preparations; and (10) recent medication changes. As a control group, 10 healthy male subjects (34 (8) years old, body mass index 26.0 (3.1) kg/cm^2) without a history of CAD or ECG evidence of an old MI were recruited for this study in New York and Osaka from October 2000 to February 2001. Exclusion criteria for healthy subjects were as follows: (1) daily intake of red wine (> 1 glass/day); (2) consumption of vitamin preparations and probucol consumers; (3) tobacco smoking.

Each participant made two visits 15 days apart. Studies were started after a 12 hour overnight fast. Patients with CAD were allowed to take their morning medications and on day 15 consumed red wine polyphenols. The study subjects were prohibited from consuming alcoholic beverages during the study and were encouraged not to change their daily diet. If patients with CAD changed their medication during the study period, they were excluded from the final analysis. The study participants were provided with red wine polyphenol powder (1.4 g/kg/day) and were instructed to drink it with water (250 ml/day). CFVR was assessed by TTDE before (baseline) and after 15 days of taking red wine polyphenols (follow up).

TTDE was performed to assess CFVR with a Sequoia digital ultrasound system (Siemens, Mountain View, California, USA) as previously described.[4 5] We first recorded the spectral Doppler signal in the left anterior descending coronary artery at rest. Adenosine was administered intravenously (0.14 mg/kg/min) for two minutes to record spectral Doppler signals to obtain the peak flow response induced by dilatation of the coronary microvessels. All patients had continuous heart rate and ECG monitoring. Systolic and diastolic blood pressures were recorded at baseline, at peak flow response, and during recovery. Mean diastolic coronary flow velocity (CFV) was measured at rest and peak flow response during drug administration. The measurements obtained in three cardiac cycles were averaged. CFVR was defined as the ratio of CFV at peak flow response to basal CFV.

All data were expressed as mean (SD). The differences between CAD and non-CAD groups for CFV and CFVR were tested by using the unpaired two tailed exact Wilcoxon test. Coronary flow data and haemodynamic data for baseline and 14 days' follow up within both CAD and non-CAD groups were compared by two tailed paired exact Wilcoxon test.

RESULTS

Table 1 shows haemodynamic and coronary flow data in both groups. Haemodynamic parameters did not change significantly at rest during 14 days of follow up in both groups. At baseline, resting CFV did not differ significantly between the groups. CFV response to drug induced hyperaemia in patients with CAD was significantly lower than that in non-CAD subjects ($p = 0.03$). Thus, CFVR was significantly lower in patients with CAD than in non-CAD subjects (3.0 (0.6) *v* 3.9 (0.3), $p = 0.005$).

In patients with CAD, no difference was observed in CFV at rest between baseline and follow up (24.5 (8.8) *v* 24.3 (7.2) cm/s). At follow up, CFV during drug administration was significantly higher than at baseline in these patients (71.8 (20.4) at baseline *v* 88.0 (25.5) cm/s at follow up, $p = 0.020$). As a result, CFVR significantly increased from 3.0 (0.6) to 3.7 (0.7) ($p = 0.004$) after patients with CAD had been taking red wine polyphenols. CFVR increased 22 (12)% in patients with CAD.

In non-CAD subjects, CFV at rest did not differ significantly between baseline and follow up (23.2 (2.1) *v* 23.0 (2.3) cm/s). CFV during drug infusion was increased at

Abbreviations: CAD, coronary artery disease; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; MI, myocardial infarction; TTDE, transthoracic Doppler echocardiography

Table 1 Change in haemodynamic and coronary flow data in patients with and without coronary artery disease (CAD)

	CAD group (n = 10)				Non-CAD group (n = 10)			
	Baseline		Two weeks		Baseline		Two weeks	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Heart rate (beats/min)								
Rest	60 (10)	60 (42–72)	61 (11)	60 (44–84)	61 (12)	60 (48–78)	63 (13)	62 (54–78)
Hyperaemia	73 (15)	75 (54–90)	71 (17)	66 (50–96)	78 (13)	82 (48–92)	82 (14)	85 (54–102)
Systolic blood pressure (mm Hg)								
Rest	127 (9)	128 (112–138)	123 (12)	127 (100–134)	120 (9)	122 (102–130)	116 (7)	116 (108–130)
Hyperaemia	12 5 (11)	127 (106–138)	118 (15)	120 (90–134)	116 (10)	119 (96–130)	113 (7)	115 (104–124)
Diastolic blood pressure (mm Hg)								
Rest	74 (10)	74 (60–88)	76 (8)	76 (66–87)	78 (6)	79 (70–90)	76 (8)	78 (60–84)
Hyperaemia	74 (8)	71 (66–88)	70 (10)	69 (56–86)	73 (8)	70 (64–90)	74 (6)	75 (60–84)
Coronary flow volume (cm/s)								
Rest	24.5 (8.8)	25.8 (12.8–43.3)	24.3 (7.2)	23.7 (13.3–35.3)	23.2 (2.1)	22.8 (20.3–27.4)	23.0 (2.3)	22.7 (20–27.8)
Hyperaemia	71.8 (20.4)	72.5 (39.8–106)	88.0 (25.5)	87.5 (51.2–123)	89.9 (12.3)	86.9 (73.8–112.3)	98.9 (12.7)**	98.8 (82.5–122.8)
CFVR	3.0 (0.6)†	3.0 (2.2–4.1)	3.7 (0.7)*	3.7 (2.8–4.9)	3.9 (0.3)	3.9 (3.5–4.7)	4.4 (0.6)***	4.3 (3.8–5.3)

*p = 0.004 *v* baseline; **p = 0.006 *v* baseline; ***p = 0.006 *v* baseline; †p = 0.005 *v* non-CAD group.
CFVR, coronary flow velocity reserve.

follow up in non-CAD subjects (89.9 (12.3) at baseline *v* 98.9 (12.7) cm/s at follow up, p = 0.006). In non-CAD subjects CFVR increased significantly after they had been taking polyphenols for 14 days (from 3.9 (0.3) to 4.4 (0.6), p = 0.006). CFVR increased 12 (11)% in non-CAD subjects.

DISCUSSION

The present study showed that coronary microcirculation was impaired in patients with CAD due to reduced CFV at peak flow response. However, CFV at peak flow response was significantly increased in both two groups after they had been taking red wine polyphenols for 14 days. Favourably, in patients with CAD CFVR increased after polyphenol intake up to the level of CFVR in non-CAD subjects before they had taken polyphenols. Thus, the present results suggest that a daily intake of red wine polyphenols may benefit both people without CAD and patients with CAD by improving the coronary microcirculation.

This study has not clarified the precise mechanism for increased CFVR after short term intake of red wine polyphenols. In a recent study analysing flow mediated brachial artery reactivity, Stein *et al*[8] showed that short term ingestion of purple grape juice improves endothelial function in patients with CAD. They suggested that improved endothelial function is the potential mechanism by which purple grape products may prevent cardiovascular events. The antioxidant effect of red wine polyphenols may improve the coronary microcirculation by improving endothelial function.

There are several limitations in this study. One is the lack of a randomised controlled group. Secondly, we obtained no evidence that endothelial function such as flow mediated dilatation of the brachial artery was improved. Lastly, we obtained no data to suggest the mechanism of reduced CFVR in patients with CAD at baseline, although one possible mechanism may be coronary microcirculation dysfunction probably caused by decreased endothelial function.

In patients with CAD, short term ingestion of red wine polyphenols improved CFVR to the level in non-CAD subjects.

ACKNOWLEDGEMENTS

We gratefully acknowledge the statistical assistance of Robert Siacca EngScD and Zhezhen Jin PhD.

Authors' affiliations

T Hozumi, K Sugioka, K Shimada, K Fujimoto, R Otsuka, H Watanabe, J Yoshikawa, Department of Internal Medicine and Cardiology, Osaka City University School of Medicine, Osaka, Japan
S H Kim, M Y Kuo, Y Miyake, S Homma, Department of Medicine, Columbia University, New York, New York, USA
K Hosoda, Institute for Fundamental Research, Suntory Ltd, Osaka, Japan

Correspondence to: Dr T Hozumi, Department of Internal Medicine and Cardiology, Osaka City University School of Medicine, 1-4-3 Asahimachi Abenoku, Osaka 545-8586, Japan; thozumi@med.osaka-cu.ac.jp

Accepted 1 September 2005

REFERENCES

1 **Frankel EN**, Kanner J, German JB, *et al*. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 1993;**341**:454–7.
2 **Kondo K**, Matsumoto A, Kurata H, *et al*. Inhibition of oxidation of low-density lipoprotein with red wine. *Lancet* 1994;**344**:1152.
3 **Miyagi Y**, Miwa K, Inoue H. Inhibition of human low-density lipoprotein oxidation by flavonoids in red wine and grape juice. *Am J Cardiol* 1997;**80**:1627–31.
4 **Nigdikar SV**, Williams NR, Griffin BA, *et al*. N. Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation in vivo. *Am J Clin Nutr* 1998;**68**:258–65.
5 **Shimada K**, Watanabe H, Hosoda K, *et al*. Effect of red wine on coronary flow-velocity reserve. *Lancet* 1999;**354**:1002.
6 **Hozumi T**, Yoshida K, Akasaka T, *et al*. Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by Doppler echocardiography: comparison with invasive technique. *J Am Coll Cardiol* 1998;**32**:1251–9.
7 **Hozumi T**, Yoshida K, Ogata Y, *et al*. Non-invasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. *Circulation* 1998;**97**:1557–62.
8 **Stein JH**, Keevil JG, Wiebe DA, *et al*. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. *Circulation* 1999;**100**:1050–5.